Institute and the Department of Veterans Affairs Cooperative Studies Program. **Results**: Genotype frequencies differed by race: CC=0.77 and CT/TT=0.23 for non-Blacks, and were 0.97(n=200) and 0.03 (n=6) for CC and CT/TT, among Blacks (p<0.001). and 0.77 (n=643) and 0.23 (n=189) for non-Blacks and did not differ by disease etiology CC=0.81 (n=483) and CT/TT=0.20 (n=122) for CC and CT/TT among the ischemics group and CC=0.83 and CT/TT=0.18 (n=73) among non-ischemics group. When analysis was restricted to ischemics, survival analysis compared among T allele carriers (CT or TT) and wild-type individuals (CC) in the ischemic group; HR=0.81, p=0.36 for CT/TT carriers. The same comparison in non-ischemics resulted in HR=1.41, p=0.28 in non-ischemics. When further restricted to non-Blacks, HR=0.78, CI=0.49-1.25, p=0.31 for ischemic CT/TT carriers and HR=1.54, CI=0.78-3.0, p=0.21 for non-ischemic carriers (p-interaction=0.10).

Conclusions: Our analysis of the BEST cohort failed to confirm previous reports of a survival benefit among CHF patients carrying the AMPD1 T allele. However, this frequency differed by race, indicating a need to explore for a possible survival advantage. C34T could not be confirmed in this larger study. Considering the difference in genotype frequencies among blacks and non-blacks, we speculate that a genetic heterogeneity might have contributed to the negative predictive value in this cohort.

1031-133 Outcomes in Diabetic Patients With Heart Failure: Impact of ACE D/I Polymorphism

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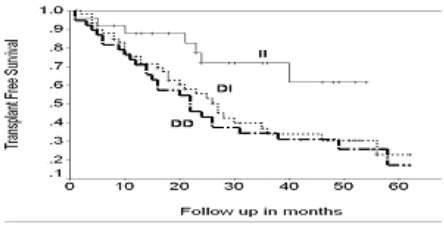
Background: Diabetes adversely affects outcomes in patients with heart failure and may interact with genetic risk. We have previously demonstrated that the Angiotensin converting enzyme deletion allele (ACE D) worsens survival in heart failure; however its impact specifically in diabetics has not been investigated. We sought to evaluate ACE D genetic risk in patients with diabetes mellitus (DM) and heart failure.

Methods: The GRACE study, a prospective single center study of genetic risk of heart failure events, enrolled 479 patients at the University of Pittsburgh between 1996 and 2001. Of the 479 patients, 122 (77% male, 84% Caucasian, 57±10 years, 60% ischemic, LVEF 0.25±0.07) had DM at baseline. Blood was obtained for DNA isolation and genotyped by standard PCR based techniques. Transplant free survival was compared in patients with diabetes based on the ACE (II/DI/DD) genotype.

Results: Patients with DM were predominantly ischemic (66% vs 45%, p<0.001) and had worse NYHA scores (class>3, 63% vs 52%, p=0.03). Event odds ratio was 2.1(p=0.001) for DM. Transplant free survival was significantly worse in patients with DM (1 year: 77%/83%, 2 year: 56%/75%, p=0.003). In the subset with DM, transplant free survival was worse in the patients with the D allele (II/DI/DD: 1 year: 88%/75%/74%, 2 year: 77%/56%/46%, p=0.03, figure)

Conclusion: In diabetics, the D allele was associated with poorer transplant free survival. The ACE genotype may play a role in the modulation of endothelial dysfunction in patients with DM.



1031-134 Relationship Between the Transcardiac Increase of Plasma Heart-Type Fatty Acid-Binding Protein and Left Ventricular Remodeling in Patients With Dilated Cardiomyopathy

Keijin Ohno, Takayoshi Tsutamoto, Chitose Ishikawa, Hiroshi Sakai, Takashi Tsutsui, Masaru Hayashi, Atsuyuki Wada, Minoru Horie, Shiga University of Medical Science, Otsu, Japan

Background; Heart-type fatty acid-binding protein (H-FABP), that is abundant in the cytosol of cardiomyocytes, transports fatty acids in cardiomyocytes. It is released rapidly from cardiomyocytes into circulating blood after myocardial damage, and serum levels are sensitive markers of myocardial infarction. However, whether plasma H-FABP level is increase in patients with dilated cardiomyopathy (DCM) remains unknown. Methods; To evaluate whether plasma H-FABP is secreted from the failing heart of DCM patients and to evaluate the relationship between transcardiac gradient of H-FABP and left ventricular function and brain natriuretic peptide (BNP), we measured plasma levels of H-FABP and BNP in aortic root and coronary sinus in 25 DCM patients with congestive heart failure and in 20 control subjects. Results; There was no difference of plasma H-FABP between aortic root and coronary sinus in the control group, but plasma H-FABP concentration was significantly higher in coronary sinus than in aortic root (3.83±0.37 vs. 4.17±0.38 ng/ml, p<0.001) in the DCM group. Plasma H-FABP level was significantly higher in the DCM group than in the control group in aortic root (3.83±0.37 vs. 2.72±0.28 ng/ml, p<0.05). There was no correlation between the transcardiac gradient of BNP and transcardiac gradient of H-FABP in patients with DCM, suggesting that the mechanism of the secretion of BNP and H-FABP is different. Transcardiac gradient of BNP correlated with left ventricular end-diastolic pressure (r=0.613, p<0.001), but did not correlated with left ventricular ejection fraction and left ventricular end-diastolic volume index (LVEDVI). Transcardiac gradient of H-FABP correlated with left ventricular end-diastolic volume index (r=0.734, p<0.0001), but did not correlated with left ventricular ejection fraction and left ventricular end-diastolic pressure. Conclusion; Plasma levels of H-FABP, one of the cardiac specific proteins, increases in patients with DCM suggest sustained ongoing myocardial damage and myocardial loss in these patients. Therefore, the increase of H-FABP may be a more sensitive marker of left ventricular remodeling (LVEDVI) than BNP in patients with DCM.

POSTER SESSION

1032 Hypertrophic Cardiomyopathy: Basic and Clinical I

Sunday, March 07, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1032-119 Prevalence of Mutations in the Cardiac Myosin-Binding Protein C Gene Among Tuscan Patients With Hypertrophic Cardiomyopathy

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Background: Mutations in the Cardiac Myosin-Binding Protein C gene (MYBPC3) represent a common cause of familial HCM. Previous studies, suggesting that hypertrophic cardiomyopathy (HCM) caused by MYBPC3 mutations often has delayed onset and benign course, are limited in number. We studied the prevalence and clinical features of HCM caused by MYBPC3 mutations in 80 consecutive, index, unrelated patients form a regional population in Tuscany. Methods: All 35 exons of MYBPC3 were screened by DHPLC followed by automatic sequencing; 100 normal controls were studied to exclude polymorphisms. Patients have been systematically followed for an average of 8.6 years. Results: We identified 17 MYBPC3 mutations in 16 patients (a 20% prevalence). Fourteen mutations were novel (IVS18+1C>T, insT753, A522T, V771M, E165D, ins/del exon 25, V189I, G531R, D786Y, R273Z, ins/del exon 31, E334K, R470W, ins/del exon 30); two (A522T and V771M) were found in compound heterozigosity in the same patient. The remaining three mutations have been previously reported (Q969X, IVS23+1A >G, R502Q). Age at diagnosis in the 16 patients with MYBPC3-related HCM was 41.3±14.6 (p=ns versus the overall group; 7 were diagnosed before age 40); maximum left ventricular (LV) thickness was 27±7 mm (range 15-38 mm); 4 (25%) had basal LV outflow obstruction (>30 mmhg). In 8 patients (50%) HCM was familial, including 4 with a family history of sudden death. At the end of follow-up, 3 patients (E165D, V189I, IVS23+1A>G; 19%) developed advanced heart failure with systolic impairment and/or restrictive LV filling pattern; one died of heart failure. An additional patient (IVS18+1C>T) had severe functional limitation due to outflow obstruction, and improved following percutaneous alcohol septal ablation. Conclusions: In a regional population from Central Italy, MYBPC3-related HCM: accounted for one fifth of consecutive unrelated patients; was often diagnosed in young patients; was often associated with progression to severe heart failure and the end-stage phase. Most of the identified mutations were novel, including two occurring in the same patient.

1032-120 Strategy for Molecular Genetic Stratification of Familial Hypertrophic Cardiomyopathy

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Background: Familial hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous disease with mutations in at least 12 large genes compromising the cardiac sarcomeres. The clinical course and prognosis vary according to the gene and specific mutation involved; identification of which would be useful in patient management and predicting other pre-symptomatic, susceptible individuals within families. Currently, no clinical genetic screening test is available for HCM. We have developed and applied an efficient, cost effective method of identifying mutations for HCM in families segregating the disease.

Methods: Seventeen members of a single family with a strong family history of sudden death and HCM were analyzed by linkage analysis using a panel of polymorphic microsatellite markers selected because they flank three of the genes most commonly associated with HCM and sudden cardiac death. Coding exons of the linked gene were then amplified by the polymerase chain reaction and sequenced in a single unambiguously affected family member. Once the pathogenic mutation was identified, all family members were genotyped for the mutation.

Results: We demonstrated linkage within the family to cardiac *Troponin T* (*TNNT*). Subsequent direct sequence analysis identified an Arg92Gln mutation that co-segregates with the clinical phenotype. This mutation is associated with aggressive disease within this family with six of 13 members dying from cardiac disease at a mean age of 35 and as young as 17. Of the seven carriers in the family, four demonstrated cardiac hypertrophy before the age of 30; the remaining three (ages 41-55) have experienced cardiac events in addition to having cardiac hypertrophy. We also definitively identified 10 genotype negative family members who are not at risk for familial HCM.

Conclusion: We describe a method for efficiently determining the genetic basis of HCM in families to allow identification of pre-symptomatic individuals and to provide prognostic information in order to develop individualized methods of surveillance and management. We demonstrate the utility in a family with a high incidence of sudden cardiac death.